TO: THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.
RE: Letter of Intent to Perform a Research Study
TITLE: Clinical Pharmacodynamics of Intravenous Etoposide and Cisplatin in Extensive Small Cell Lung Cancer

Problem and Plans:

Pharmacokinetic studies are now accepted research tools to define the disposition of anticancer agents in a selected group of patients. From these studies large inter-patient variability has become an apparent problem. Since anticancer agents have a narrow therapeutic range and are often used at near maximally tolerated doses, measurements of these agents may be as useful in routine clinical practice as for other drugs.

Although pharmacokinetic values have been established for most anticancer agents, their routine application has been hampered by the need for numerous samples and time consuming laboratory procedures. Therefore, the first objective of this study is to establish optimal sampling strategies for two commonly used anticancer agents, etoposide and cisplatin, in patients with small cell lung cancer. Once a model for the estimation of pharmacologic values is established, pharmacokinetics can be evaluated in a broader clinical investigation.

There is currently a gap between pharmacokinetic modeling and its clinical application. The main objective is to close this gap and to evaluate the pharmacodynamics (relationship between drug kinetics and clinical outcome) of etoposide and cisplatin in patients with small cell lung cancer. The hypothesis is that the variability of pharmacological values (eg. area under the concentration versus time curve and clearance rates) has a direct impact on host toxicity and tumor response. If a correlation between a pharmacokinetic variables such as drug clearance and clinical outcome can be demonstrated, then patients can be treated on the basis of their individual drug disposition and clearance to optimize the exposure to etoposide and cisplatin in order to achieve an optimal effect on small cell lung cancer.

The specific plans for this program are:
- Clinical trial of intravenous etoposide and cisplatin in patients with extensive small cell lung cancer.
- Investigate pharmacokinetics of both drugs and devise strategy for optimal sampling.
- Correlate pharmacokinetic values with host toxicity and tumor response, i.e. evaluate for pharmacodynamic correlations.

The clinical efficacy of a cancer chemotherapeutic agent, the sum total expression of its toxicity, selectivity, specificity, as well as its pharmacokinetic and pharmacodynamic properties in man, is often exquisitely sensitive to manipulations of dose, schedule, and route of administration. To elicit the most favorable clinical response through such manipulations, it is desirable not only to determine the ensuing pharmacokinetic changes, but also to correlate the results with the pharmacodynamics of the agent.

This study should help establish optimal sampling strategies and demonstrate pharmacodynamic correlations. Results from this study may serve as a guide for individualized dosage regimens for future patients with small cell lung cancer.

Hypothesis: Differing Individual Drug Disposition Predicts Clinical Outcome
Size of Project: Clinical study with 60 patients over 3 years.
Anticipated Duration: 3 years (1 year with 2 renewals)
Anticipated Cost: $70,000 per year